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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,057	10/24/2003	Joost A. Kolkman	A-1217-US-CIP3	1548

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
01/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/693,057	KOLKMAN ET AL.
	Examiner	Art Unit
	Sue Liu	1639

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31 and 33-49* is/are pending in the application.

4a) Of the above claim(s) *34-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claim Status

2. Claims 1-24 and 32 have been cancelled as filed 10/31/07.

Claims 42-49 have been added as filed on 10/31/07.

Claims 25-31 and 33-49 are currently pending.

Claims 34-49 have been withdrawn.

Claims 25-31 and 33 are being examined in this application.

Election/Restrictions

3. Applicant's election with traverse of Group I invention (Claims 25-33) in the Reply filed on 8/15/06 is as previously acknowledged.

4. Applicants elected the following species:

A. A single species of a target molecule. Applicants elect “IgE”.

B. A single species of a first monomer domain. Applicants elect an "LDL receptor class A monomer domain".

C. A single species of a second monomer domain. Applicants elect an "LDL receptor class A monomer domain".

D. A single species of a third monomer domain. Applicants elect an "LDL receptor class A monomer domain".

in the Reply filed on 8/15/06 is as previously acknowledged. The newly added claims (claims 42-49) are drawn to non-elected species (i.e. C2 monomer domains). Thus, the instant claims 42-49 have been withdrawn due to non-elected species.

Priority

5. This application is a CIP of 10/289,660 (filed on 11/06/2002; now ABN), which is a CIP of 10/133,128 (filed 04/26/2002), which claims benefit of the following provisional applications:

60/374,107 04/18/2002;

60/333,359 11/26/2001;

60/337,209 11/19/2001;

60/286,823 04/26/2001.

6. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-

filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/286,823, filed on 4/26/01, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. For example, the '823 provisional patent does not provide support for LDL-receptor Class A domain and domains having 30-100 amino acids. The current application obtains the priority date of 60/337,209.

Thus, the effective filing date of the instant application is 11/19/01.

Claim Rejections Withdrawn

7. In light of applicants' amendments to the claims to recite "LDL-receptor class A monomer domain" and supporting arguments, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 25-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

B.) Claims 25-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating libraries of monomers and/or multimers based on LDL receptor A domains alone, and C2 domains alone, does not reasonably provide enablement for generating other proteins that comprise any other monomers and/or multimers.

C.) Claims 25, 27, 28, 30, 31, and 33 are rejected under **35 U.S.C. 102(b)** as being anticipated by Barbas et al (US 6,140,466; 10/31/2000).

D.) Claims 25-31 and 33 are rejected under **35 U.S.C. 102(e)** as being anticipated by Etzerodt et al (US 2004/0132094 A1; 7/8/2004; priority date: 2/28/2001).

E.) Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15-17, and 20-26 of copending Application No. 11/281,256 (20060234299; filed 11/16/05).

F.) Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 11/281,245 (20060223114; filed 11/06/2005).

8. Due to the abandonment of the co-pending application (10/966,064) and cancellation of the pertinent claims in the 10/871,602 application, the following claim rejections are withdrawn:

A.) Claim 25 and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 207-214 of copending Application No. 10/966,064 (20050221384; filed 10/15/04).

B.) Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 21, 29, 33, 36, 78, and 98 of copending Application No. 10/871,602 (20050089932; filed 6/17/04).

9. Upon further consideration, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-32 of copending Application No. 10/971,679 (20050164301; filed 10/22/04).

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

<u>Esser</u>

11. Claims 25-30 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988; cited previously). The previous rejection over claim 32 is moot due to applicant's cancellation of said claim. The previous rejection over claims 25-30 and 33 is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below.

The instant claims recite a method for identifying a multimer that binds to a target molecule, the method comprising, providing a library of polypeptides, the polypeptides comprising LDL-receptor class A monomer domains, wherein the monomer domains consist of

30-100 amino acids; screening the library of polypeptides for affinity to a target molecule, identifying at least one polypeptide comprising a first LDL-receptor class A monomer domain that specifically binds to a target molecule; linking the first LDL-receptor class A monomer domain to a plurality of additional LDL-receptor class A monomer domains to form a library of LDL-receptor class A multimers, the multimers comprising the fast monomer domain and one of the plurality of additional monomer domains; screening the library of multimers for the ability to bind to the target molecule; and identifying a multimer that specifically binds to the target molecule.

Esser et al, throughout the publication, teach mutational analysis of the ligand binding domain (reading on LDL receptor class A monomer domains of **clm 25**) of the human LDL lipoprotein receptor (see Figure 1), which indicates that each of the cysteine rich repeats of the LDL receptor has around 40-70 amino acids. The LDL receptor repeats and/or combination of the repeats read on the monomers, and the multimers of **clm 25**, and the trimer of **clm 33**. The reference's teaching also read on the step of providing a library of polypeptides as recited in **clm 25**.

The reference also teaches that the LDL receptor binds to various ligands (such as ApoB-100 of LDL and ApoE) through the cysteine-rich repeat regions (corresponding to the LDL receptor class A monomer domains), which reads on the protein target molecule of **clm 25 and 29**.

The reference teaches that the LDL receptor A domains are identified (read on the method steps of "screening" and "identifying" of **clm 25**), different mutations are generated in

different A domains (or monomers) that are encoded by polynucleotides (see Figure 1 and p. 13283, right col.), and each of the LDL receptor binding domain comprises multiple A monomer domains (see Figure 1, i.e. repeats 1-7 linked together), which read on the linking of an identified monomer with a plurality of different monomers (the repeats with different mutations) to form multimers (such as trimers), and screening for target binding multimers of **clms 25 and 33**, as well as polynucleotides of **clm 30**. The generated multiple polypeptides would read on the library of polypeptides of the instant claim. The reference teaches assaying the binding of the polypeptides with various ligands, which assaying steps read on "screening the library" for binding to a target molecule.

The reference also teaches that mutations in different cysteine-rich sequences (the different monomer domains) lead to different binding specificity to different ligands (see Abstract, Tables I and II, and p. 13287+ of the reference), which reads on the increased binding specificity of **clm 28**.

It is known in the art that the six cysteine residues in each of the cysteine-rich repeats (monomer domains) inherently form disulfide bonds as evidenced by Fass et al (Nature. Vol. 388: 691-693; 1997; cited previously), and therefore the structure taught by the reference (Esser et al) reads on the disulfide bond and six cysteines of **clms 26 and 27.**

<u>*Discussion and Answer to Argument*</u>

12. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state "Esser, et al., do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule." (Reply, pp.12-13).

Applicants have made the above allegation without providing any reason or rationale as to why the teaching of the Esser reference does not anticipate the claimed inventions. Applicants briefly stated applicant's interpretation of the reference's teaching. However, applicants have not pointed out the supposed difference between the reference's teachings and the instant claimed invention. In other words, applicants have not provided any reasons and/or evidence to show how the cited reference does not anticipate the instant claimed invention.

As discussed in the previous office as well as the discussion above, the teaching of the Esser reference anticipates the claimed invention. Applicants are respectively directed to the above rejection for detailed discussion of the reference's teachings.

Applicants also argue that the reference does not teach "walked" libraries or methods of using them to identify a multimer (or any molecule) that binds to a target molecule. (Reply, p.14, para 3).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "walked multimer library") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

<u>*Bajari*</u>

13. Claims 25-31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bajari et al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept., 1998; cited previously). The rejection previous over claim 32 is moot due to applicant's cancellation of said claim. The previous rejection over claims 25-31 and 33 is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below.

Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domain (LR8 fragments) or variants thereof that bind to a protein target (see Abstract), which read on the screening method of **clm 25**.

The reference teaches the LR8 fragment of the LDL receptor is the LDL receptor type A domain (p. 379, right col.), which reads on LDL receptor class A monomer domains of **clms 25**. The reference also teaches the LR8 repeats have more than 30 amino acid residues, and have six cysteines (see Figures 1 and 2; p. 1055, left col.). The LR8 repeats and/or combination of the

repeats read on the monomers, and the multimers of **clm 25**, the trimer of **clm 33**, and the six cysteines of **clm 27**.

The reference also teaches disulfide bridges (or bonds) formed by the six cysteine residues (p. 1058, right col., middle of para 1), which reads on the disulfide bonds of **clm 26**.

The reference also teaches that the screening (or panning target) is receptor associated protein (RAP) (Abstract and p. 1059, left col., para 2), which reads on the protein target molecule of **clm 25 and 29** as well as the screening steps of the instant **clm 25**.

The reference teaches that the LDL receptor A domains are identified (reads on the "screening" and "identifying" steps of **clm 25**, different mutations are generated in different A domains (monomers or repeats) that are encoded by polynucleotides (p. 1059, left col.) and each of the LDL receptor proteins containing multiple A monomers or different combinations of various A domains (e.g. Figure 2; p.1058, para 2), which read on the linking of an identified monomer with a plurality of different monomers (the repeats with different random mutations) to form multimers (such as trimers), and screening for target binding multimers of **clms 25 and 33**, as well as polynucleotides of **clm 30**.

The reference also teaches that isolated LR8 domains have high affinity to the ligand (p.1057, right col., and pp. 1055-1056, bridging para), which reads on inherent property of increased binding specificity of the multimers of **clm 28**.

The reference teaches the library has 10^8 phages (containing different polypeptides), and isolation of 120 phage clones (p. 1055, left col.), which reads on the at least 100 different polypeptides of **clm 31**.

Discussion and Answer to Argument

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state "Bajari, et al., do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule." (Reply, p.13, para 2).

Applicants have made the above allegation without providing any reason or rationale as to why the teaching of the Bajari reference does not anticipate the claimed inventions. Applicants briefly stated applicant's interpretation of the reference's teaching. However, applicants have not pointed out the supposed difference between the reference's teachings and the instant claimed invention. In other words, applicants have not provided any reasons and/or evidence to show how the cited reference does not anticipate the instant claimed invention.

As discussed in the previous office, the teaching of the Bajari reference anticipates the claimed invention. Applicants are respectively directed to the above rejection for detailed discussion of the reference's teachings.

Applicants also argue that the reference does not teach "walked" libraries or methods of using them to identify a multimer (or any molecule) that binds to a target molecule. (Reply, p.14, para 3).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "walked multimer library") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

<u>*Esser and Bajari*</u>

16. Claims 25-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari et

al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept., 1998). The previous rejection over claim 32 is moot due to applicant's cancellation of said claim. The previous rejection over claims 25-31 and 33 is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below.

Esser et al, throughout the publication, teach mutational analysis of the ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor, as discussed supra.

Esser et al do not explicitly teach the at least 100 different polypeptides comprising the monomers and/or multimers, as recited in **clm 31**.

However, Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domains (LR8 fragments) or variants thereof that bind to a protein target, as discussed above. The reference also teaches the display library contains at least 100 different polypeptides, as discussed above. In addition, the reference teaches the advantages of screening large libraries such as the approach would allow developments of diagnostics and/or therapeutics of interest (Abstract of the Bajari reference). The reference further teaches the screening of phage libraries (containing a large number of polypeptides) would allow isolation of high affinity polypeptides that are in soluble form (p. 1057, last para).

Due to the fact that Bajari teaches the advantages and the need to screen large libraries to isolate polypeptides of interest, a person of ordinary skill in the art would have been motivated at the time of the invention to screen large libraries of polypeptides (at least 100 polypeptides) to isolate the desired polypeptides with high target binding affinity. A large library contains more

diverse polypeptides as taught by Bajari (10^8 phages; p. 1055, left col.), and thus would allow higher probability of success of isolating a desired target.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Bajari et al have demonstrated the success of screening libraries of monomers (LDL receptor A domains) containing at least 100 different polypeptides.

Discussion and Answer to Argument

17. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants also argue that the reference does not teach "any 'walked' libraries or any methods of using such walked libraries". (Reply, p.15, para2).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "walked libraries") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants also argue that the method "walked libraries" or "any methods of using such walked libraries" are recited in the instant claims. Applicants state the followings:

"The claimed invention (independent claims 25 and 42) includes the step of *linking the first (C2 or LDLR) monomer domain to a plurality of additional (C2 or LDLR)...monomer*

domains. This step is the essence of the walked library approach described in the specification..." *(Reply, p.15, para 3).*

It is initially noted that the instant claim 42 is withdrawn from further consideration due to non-elected species.

Applicants have not specifically pointed out the specific support in the instant specification for the asserted definition or description of the phrase "walked libraries". The instant specification does not specifically define the term "walked libraries" to mean the method step recited by applicants in the Reply (also recited in italic above).

As discussed above in the body of the above rejections (see the 102 rejections over the Esser and Bajari references), both of the references teach polypeptides comprising multiple LDL receptor A monomer domains (or "repeats"), which the method of making these polypeptides read on linking step of the instant claim because the monomer domains are "linked" together.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

'723

19. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-10, 16, 23, 29, 33, 36, and 98 of copending Application No. 10/840,723 (20050053973; filed 5/5/2004). The previous rejection is maintained for the reasons of record as set forth in the previous Office action.

Discussion and Answer to Argument

20. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the provisional ODP rejection should be withdrawn because no other rejections are remaining. (Reply, p.17, para 1).

However, the instant claims are remain rejected, and thus the above ODP rejection is maintained for the reason of record.

'351

21. Claim 25, 26, and 28-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18, 21-24, 29-31, 34 and

36 of copending Application No. 10/957,351 (20060008844; filed 1/12/2006). The previous rejection is maintained for the reasons of record as set forth in the previous Office action.

<u>Discussion and Answer to Argument</u>

22. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the provisional ODP rejection should be withdrawn because no other rejections are remaining. (reply, p.16, para 7).

However, the instant claims are remain rejected, and thus the above ODP rejection is maintained for the reason of record.

<u>'989</u>

23. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 18-21, and 24-27 of copending Application No. 11/155,989 (20060177831; filed 6/17/05). The previous rejection is maintained for the reasons of record as set forth in the previous Office action.

<u>Discussion and Answer to Argument</u>

24. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the provisional ODP rejection should be withdrawn because no other rejections are remaining. (reply, p.16, para 7).

However, the instant claims are remain rejected, and thus the above ODP rejection is maintained for the reason of record.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

<u>Barbas and Russell</u>

26. Claims 25-31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (US 6,140,466; 10/31/2000; cited previously), in view of Russell et al ((Journal of Biological Chemistry. Vol. 264 (36): 21682-21688; 1989; cited previously).

Barbas et al, throughout the patent, teach identifying or generating zinc finger polypeptides (reads on polypeptides comprising monomers and multimers) that bind to specific target nucleotides (Abstract of the reference).

The instant specification defines the term “monomer domain” or “monomer” broadly to encompass any “discrete region found in a protein or polypeptide” that can specifically bind to a

target molecule (p. 21 of the spec.), and the monomer domain can be of any size (p. 32, [133]). Thus, any segment of polypeptide or protein that can bind to a target molecule is a "monomer" or a "monomer domain" as defined by the instant specification.

The zinc finger containing proteins taught by Barbas et al have "discrete regions" such as the different zinc finger regions (Figure 8A of Barbas), which either the individual "Fingers" (1-3) or the combination of the "Fingers" is a monomer domain according to the definition of the instant disclosure. The instant specification also discloses "zinc finger" as an example of "monomer" or "monomer domain" (p. 2, [20] of the instant spec.). Thus, the zinc finger regions taught by Barbas et al reads on the monomer domains of 30-100 amino acids of **clm 25**. As indicated by Figure 8 of the Barbas reference, "finger 1" has about 30 amino acids, and the combination of fingers 2 and 3 has about 60 amino acids. Furthermore, the reference also teaches a linker fused two three-finger proteins and multi-finger proteins (Abstract and Example 13 at col. 15, lines 20+ of Barbas), which each of the individual fingers and/or the combination of fingers (such as a two finger domain of about 60 amino acids) read on a monomer domain that has 30-100 amino acids.

Barbas et al also teach generating libraries of zinc finger proteins (through molecular cloning) and screening the libraries of zinc finger protein against nucleic acid target through binding assays (See Examples 1-14, especially, Examples 3 and 13), which reads on the screening of the library of polypeptides for affinity to a target molecule of **clm 25**, and the polynucleotides encoding the polypeptides of **clm 30**.

The reference teaches the generation of phage display library of zinc finger proteins with the size of $5X10^7$ PFU (col. 40, lines 30+), which reads on at least 100 different polypeptides of **clm 31**.

Barbas also teaches randomization of amino acid residues only in the "finger 3" region of the zinc finger protein (Example 3 of Barbas), and thus holding other regions in the protein constant. The reference also teaches multiple panning procedures comprising several rounds of nucleic acid target recognition and replication (cols. 40-41). These read on linking the first monomer domain to a plurality of different monomer domains, forming multimers, and screening multimers against the target molecule of **clm 25**.

The reference teaches each of the zinc fingers of the zinc finger protein contains two cysteine residues (col. 1, lines 43+). The reference also teaches polypeptides comprising multiple "fingers" such as 3-12 fingers (col. 50, lines 30+), and thus a combination of three fingers that constitute as a "monomer" having six cysteines, as recited in **clm 27**.

The reference also teaches improved affinity for binding the target nucleic acid sequence of the mutated zinc finger protein (multimers) (col. 48, lines 32+), which reads on the increased affinity of **clm 28**.

The reference also teaches linking the zinc finger protein (with different numbers of monomers) to other protein domains (such as Jun/Fos leucine zippers and/or additional zinc fingers), and screening against target nucleic acid binding (see Examples 12-14), which reads on the trimers screening of **clm 33**.

Barbas et al do not explicitly teach the monomer domains are "LDL receptor class A monomer domains" (with at least two disulfide bonds) as recited in **clms 25** and **26**. The Barbas reference also does not explicitly teach the target molecule is a protein as recited in **clm 29**.

However, Russell et al teach mutations in different LDL receptor A monomer domains that created LDL receptor proteins with altered (decreased or increased) ligand binding abilities (e.g. p.21684, Figure 2; Table II). In addition, the Russell reference teaches the need to conduct further mutagenesis experiments (e.g. p.21687, col.2, para 1). The Russell reference also explicitly teaches "The current findings suggest that a multiplicity of cysteine-rich repeats may allow a single protein to bind several different protein ligands by employing different combinations of repeats" (Abstract). Thus, one of ordinary skill in the art would have been motivated to combine the different mutant "repeats" (or A monomer domains) from the Russell reference to arrive at LDL receptor proteins with different binding abilities that are capable of binding different ligands. In addition, the LDL receptor A monomer domain inherently possesses as least two disulfide bonds, and protein target binding properties as discussed supra.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to screen for polypeptides comprising various "monomers" such as LDL receptor A monomer domains for specific target binding ability.

A person of ordinary skill in the art would have been motivated at the time of the invention to use polypeptides comprising various LDL receptor A monomer domains to screen for polypeptides with specific target binding property, because making and screening for polypeptides with specific target binding properties are known and routine in the art as taught by Barbas et al and Russell et al. Both of the Barbas and Russell references teach methods of

making various polypeptides comprising multiple "monomers", it would have been obvious to one skilled in the art to substitute one type of "monomer" (e.g. zinc fingers with LDL-receptor A monomer) for the other to achieve the predictable result of screening for a target binding polypeptide.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Barbas and Russell references have demonstrated the various applicability of preparing, screening and identifying polypeptides with various target binding properties.

Etzerodt and Russell

27. Claims 25-31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etzerodt et al (US 2004/0132094 A1; 7/8/2004; priority date: 2/28/2001; cited previously), in view of Russell et al ((Journal of Biological Chemistry. Vol. 264 (36): 21682-21688; 1989; cited previously).

Etzerodt et al, throughout the publication, teach libraries of proteins that comprise C-type Lectin-like domains, and the methods of generating such libraries (see Abstract of the reference).

The reference teaches the C-type lectin-like domains (CTLDs) has approximately 50 to 70 amino acid residues, as indicated by Table 1 and Figure 1 of the reference (p. 2-3 and [0007]), which the CTLDs read on the monomer domains of **clm 25** as defined by the instant specification (see the discussion above regarding the definition for "monomer").

The reference teaches generating libraries of proteins that comprise mutant CTLDs (p. 18, [0176]+) and screening the library against target molecules ([0188]), which reads on the screening of the library of polypeptides comprising different monomer domains of **clm 25**.

The reference teaches that the protein libraries are generated based on tetranectin CTLD and the tetranectin is trimeric in nature ([0046] and [0192]), and generation and screening of multimeric libraries ([0071])-[0076]; and Claims 1-29; especially Claims 10 and 13), which read on the screening of multimers and trimers of **clms 25 and 33**.

The reference teaches the CTLDs contain six cysteine residues (see Figure 1), and contain two or three intra-chain disulfide bridges (or bonds) ([0004]), which read the disulfide bond of **clm 26** and the six cysteines of **clm 27**.

The reference teaches screening the combinatorial libraries (monomer or multimer libraries) based on affinity selection, and "isolating progressively better binder by repeated rounds of panning and re-amplification (Claim 29 of the reference), which read on the increased affinity of **clm 28**.

The reference teaches the CTLDs (such as tetranectin) bind to various targets including plasminogen, fibrinogen/fibrin, and apolipoprotein, which reads on the target is a protein of **clm 29**.

The reference teaches the libraries of polypeptides are encoded by polynucleotides (Claim 22 of the reference), which reads on the polynucleotides of **clm 30**.

The reference teaches the sizes (such as 10^{11}) of the phage display libraries used to express the libraries of polypeptides ([0225]), which reads on at least 100 different polypeptides of **clm 31**.

Etzerodt et al do not explicitly teach the monomer domains are "LDL receptor class A monomer domains" (with at least two disulfide bonds) as recited in **clms 25**.

However, Russell et al teach mutations in different LDL receptor A monomer domains that created LDL receptor proteins with altered (decreased or increased) ligand binding abilities (e.g. p.21684, Figure 2; Table II). In addition, the Russell reference teaches the need to conduct further mutagenesis experiments (e.g. p.21687, col.2, para 1). The Russell reference also explicitly teaches "The current findings suggest that a multiplicity of cysteine-rich repeats may allow a single protein to bind several different protein ligands by employing different combinations of repeats" (Abstract). Thus, one of ordinary skill in the art would have been motivated to combine the different mutant "repeats" (or A monomer domains) from the Russell reference to arrive at LDL receptor proteins with different binding abilities that are capable of binding different ligands. In addition, the LDL receptor A monomer domain inherently possesses as least two disulfide bonds.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to screen for polypeptides comprising various "monomers" such as LDL receptor A monomer domains for specific target binding ability.

A person of ordinary skill in the art would have been motivated at the time of the invention to use polypeptides comprising various LDL receptor A monomer domains to screen for polypeptides with specific target binding property, because making and screening for polypeptides with specific target binding properties are known and routine in the art as taught by Etzerodt et al and Russell et al. Both of the Etzerodt and Russell references teach methods of making various polypeptides comprising multiple "monomers", it would have been obvious to

one skilled in the art to substitute one type of "monomer" (e.g. zinc fingers with LDL-receptor A monomer) for the other to achieve the predictable result of screening for a target binding polypeptide.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Etzerodt and Russell references have demonstrated the various applicability of preparing, screening and identifying polypeptides with various target binding properties.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
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1/17/08